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Assessment of preparation time with fully-liquid versus non-fully liquid paediatric hexavalent vaccines. A time and motion study

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ABSTRACT

Background and aims: Simplified vaccine preparation steps would save time and reduce potential immunisation errors. The aim of the study was to assess vaccine preparation time with fully-liquid hexavalent vaccine (DTaP-IPV-HB-PRP-T, Sanofi Pasteur MSD) versus non-fully liquid hexavalent vaccine that needs reconstitution (DTPa-HBV-IPV/Hib, GlaxoSmithKline Biologicals).
Methods: Ninety-six Health Care Professionals (HCPs) participated in a randomised, cross-over, open-label, time and motion study in Belgium (2014). HCPs prepared each vaccine in a cross-over manner with a wash-out period of 3–5 min. An independent nurse assessed preparation time and immunisation errors by systematic review of the videos. HCPs satisfaction and preference were evaluated by a self-administered questionnaire.
Results: Average preparation time was 36 s for the fully-liquid vaccine and 70.5 s for the non-fully liquid vaccine. The time saved using the fully-liquid vaccine was 34.5 s ($p \leq 0.001$). On 192 preparations, 57 immunisation errors occurred: 47 in the non-fully liquid vaccine group (including one missing reconstitution of Hib component), 10 in the fully-liquid vaccine group. 71.9% of HCPs were very or somewhat satisfied with the ease of handling of both vaccines; 66.7% and 67.7% were very or somewhat satisfied with speed of preparation in the fully-liquid vaccine and the non-fully liquid vaccine groups, respectively. Almost all HCPs (97.6%) stated they would prefer the use of the fully-liquid vaccine in their daily practice.
Conclusions: Preparation of a fully-liquid hexavalent vaccine can be completed in half the time necessary to prepare a non-fully liquid vaccine. The simplicity of the fully-liquid hexavalent vaccine preparation helps optimise reduction of immunisation errors.

1. Introduction

Combination vaccines have several benefits for the vaccine, the physician, the society, the healthcare system and public health. By delivering more antigens in fewer injections, combination vaccines can provide better coverage and timeliness of vaccination, improve the efficiency of the programme and reduce costs for the healthcare system [1].

Time spent by Health Care Professionals (HCPs) during vaccine preparation is a component of the overall programmatic cost associated with vaccine administration. Even if limited for one vaccination (approximately 25% of the overall vaccination time [2]), this time can be decreased by adapting devices and may have a larger impact when applied to large populations. For instance, vaccines could be administered 37.3 s quicker using prefilled syringes compared to multidose vials [3] and 46 s quicker using a fully-liquid DTP-HepB-Hib combination vaccine[1] compared to a non-fully liquid combination vaccine comprising of one vial of liquid DTwP–HepB and one vial of lyophilised Hib requiring reconstitution[2] [2]. Another important aspect for success of immunisation programmes is the quality with which vaccines are administered [4]. Proper vaccine handling and preparation is

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[1] Trade name: Easyfive®.
[2] Trade names: Tritanrix® and Hiberix®.

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critical in maintaining the integrity of the vaccine during transfer from the manufacturer's vial to the syringe and ultimately to the patient. Guidelines have been developed to assist HCPs in following up-to-date immunisation standards [5,6]. In Belgium, the National Immunisation Technical Advisory Group (NITAG) provides recommendations for vaccination; based on the NITAG recommendations, Regional Advisory Groups (e.g. the Flemish Vaccination Platform) determine the yearly immunisation vaccination schedule. Practical immunisation trainings are offered in some medical and paramedical curricula. However, in-service training is only offered to the personnel of well-baby clinics and school health centres. Adapting devices can contribute to avoid, reduce or mitigate errors in immunisation and associated impact on safety [7].

A hexavalent vaccine (DTPa-HBV-IPV/Hib, GlaxoSmithKline Biologicals[3]), supplied as powder and suspension for reconstitution and indicated for primary and booster vaccination of infants against diphtheria (D), tetanus (T), pertussis (aP), hepatitis B (Hep B), poliomyelitis (IPV) and disease caused by *Haemophilus influenzae* type b (Hib) has been available in Europe for over a decade. Lyophilised Hib-PRT-T is reconstituted with a syringe containing the D, T, aP, IPV and Hep B components used as a diluent.

In 2013, a fully-liquid (prefilled syringe), ready-to-use hexavalent vaccine (DTaP-IPV-HB-PRP-T, Sanofi Pasteur MSD[4]) was granted marketing authorisation in Europe. This vaccine is indicated for primary and booster vaccination of infants and toddlers from 6 weeks to 24 months of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by Hib. At the time of this study only the non-fully liquid combination vaccine was available in Belgium.

Time and motion studies (T&M) require an independent and continuous observation and are, as such, a more precise method than self-reporting or work sampling techniques, which collects data at intervals of time. In medical care, T&M studies are efficiently used to determine the timing and duration of tasks or procedures [8]. T&M studies are generally small due to the high resource demands of conducting independent and continuous field observations. This can potentially exacerbate an effect of observer biases and imposes a higher requirement on both subject-selection and subject-observer assignment. Furthermore, a change in subject behaviour may occur following the continuous observation of that subject performing a task. Methods have been developed to limit the potential effect of these biases. Recording HCPs' activities on video has recently been used to prevent the observer effect [9,10] and can also allow the observer to replay each and every task for review and analysis, thus improving the quality of data.

Using a T&M study design, the main objective of this study was to assess vaccine preparation time of fully-liquid hexavalent vaccine versus non-fully liquid hexavalent vaccine that requires reconstitution prior to administration. The study also assessed the risk of immunisation errors, the satisfaction and preference of HCPs in charge of paediatric vaccination when using both vaccines.

2. Methods

2.1. Study design

The study was a cross-over, randomised, open-label study conducted in 4 different cities in Belgium: Brussels, Liège, Charleroi and Namur (Fig. 1).

Study participants were required to prepare consecutively a fully-liquid as well as a non-fully liquid vaccine (or in the opposite order), with at least a 3 to 5 min wash-out period between preparations. Vaccines were displayed on a tray along with an asepsis set to be used at HCPs' discretion in accordance with their usual practice. The first vaccine to be prepared was randomly determined. Randomisation was stratified by site and balanced every two participants.

Both vaccine preparations were recorded using video equipment allowing for time capture. Immediately after preparation of both vaccines, HCPs were asked to complete a self-administered questionnaire on their preference and satisfaction regarding the two vaccines.

2.2. Participants

In order to reflect usual practice in Belgium and different user profiles, HCPs recruited in the study were a combination of General Practitioners (GPs), paediatricians, youth health doctors and nurses. They had to have more than 2 years of experience in paediatric vaccination and to administer or prepare at least 3 childhood vaccines per week, including at least one hexavalent vaccine. Prior specific training on vaccine preparation and administration was collected for analysis purposes but were not a pre-requisite for participation in the study. HCPs having a permanent position within pharmaceutical industry or refusing video capture were excluded.

Phone book lists were used to contact HCPs of different specialties in the geographical area of cities concerned by the study.

2.3. Setting and bias control

Bias prevention steps included:

- Development of standard scripts for study presentation to the participants to decrease selection bias. The sponsor name was systematically concealed until the end of the study procedures.
- A cross-over design to neutralise the effect of video/observer presence between vaccine preparations.
- On-site study personnel trained to avoid any influence on HCPs during vaccine preparation processes.
- Defined start and stop of vaccine preparation time.
- Randomisation of the vaccine preparation sequence and the order of questions on the self-administered questionnaire.
- Study execution outside the usual HCPs working premises, in a central location of each city to provide a neutral unity of place, time and action.
- Vaccine preparation time assessment in a short period of time to prevent time-effect bias.
- Presentation of both vaccines outside their packaging and without leaflet. Thus, avoiding any impact on preparation time due to potential HCP distraction towards packaging leaflets of an unknown vaccine (the fully-liquid vaccine was not yet marketed in Belgium at time of study conduct).

Given the cross-over design of the study and in order to take into account real life conditions of use (including different levels of experience), representativeness or homogeneity of the HCP sample was not required.

2.4. Outcome measures and data collection

2.4.1. Vaccine preparation

An independent HCP (nurse) was trained to assess the time taken for vaccine preparation and immunisation errors by reviewing the videos recorded during each assessment. Training included study methods and video review processes. A physician performed data quality control by reviewing a random sample of 10% of the videos. The quality control concerned preparation time and

[3] Trade name: Infanrix® hexa.
[4] Trade name: Hexaxim®/Hexyon®/Hexacima®.

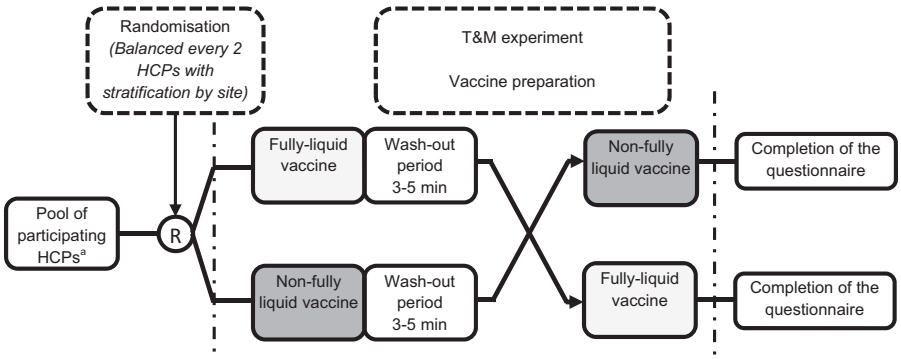

Fig. 1. Study design. [a] Consistent with local usual practice in terms of HCP specialty; combining different levels of experience.

immunisation errors identification as well as any issue identified by the nurse.

2.4.1.1. Vaccine preparation time. Vaccine preparation time was defined as the period of time between when HCP first touched the materials on the experimental field (e.g. syringe, vial or needles) and when he landed down the syringe ready for administration. It excluded the time necessary to obtain vaccine from storage, administration of vaccine, disposal of vial, syringe, needle, and documentation of vaccine administration. To validate and harmonise visual references for start and stop of vaccine preparations and identification of immunisation errors, the first 10% of the videos were reviewed twice, first by the nurse and then by the physician. Minutes and seconds (s) were recorded.

2.4.1.2. Immunisation errors. Immunisation errors were defined as: asepsis fault, needle stick, liquid leakage, failure to purge syringe by the end of preparation process, missed reconstitution of Hib-PRP-T (non-fully liquid vaccine only), failure to draw up the entire content of Hib-PRP-T vial in the syringe (non-fully liquid vaccine only). Any other unexpected immunisation errors/incidents observed during vaccine preparation were also recorded.

2.4.2. HCPs satisfaction and preference

Satisfaction with vaccine ease-of-handling and speed of preparation was collected using a 5-point Likert scale (very satisfied/somewhat satisfied/neutral/not very satisfied/not at all satisfied). HCPs were then asked to indicate between the two hexavalent-vaccine forms the one they would prefer to use in their childhood vaccination daily practice.

2.5. Ethics, data privacy and pharmacovigilance

The study was approved by the ethics committee of University Hospital Antwerpen, Belgium.

In this study, vaccines were not administered to patients and no health data were collected. All data collected were managed in accordance with local data privacy regulations.

Written informed consent was obtained from each HCP prior to study start.

A reporting process for potential adverse events or incidents related to study vaccines or in relation with their handling during preparation was established prior to study start.

2.6. Statistics

Previously published data demonstrated an approximately 50% decrease in time necessary to prepare a fully liquid vaccine (36 s) compared to a lyophilised one (75 s) [2]. Considering a paired test and under the assumption of a standard deviation (SD) of 75, 77 HCPs were estimated to be sufficient to demonstrate highly significant difference of 50% of time savings with a power of 90% and a level of significance of 0.01. It was decided prior to study implementation to include a sample of 100 HCPs to maintain the possibility, depending on the SD value, of discussing study results on HCP specialty and number of weekly vaccination.

Differences in time of vaccine preparation were assessed by a Wilcoxon paired test.

Data were entered using ClinInfo® (Lyon, France) and data analysis was performed in SAS® software version 9.2 (SAS Institute Inc., Cary, USA).

3. Results

3.1. Study sample

Of the 100 HCPs who agreed to participate, 96 HCPs came to the study site. All HCPs completed the experiment and the questionnaire.

The mean (SD) age of HCPs was 44.5 years (12.7) (Table 1). Of the 96 HCPs, 50 (52.1%) were paediatricians, 34 (35.4%) were GPs and 12 (12.5%) were nurses. Besides, 54 (56.3%) performed at least 10 vaccinations (childhood or adult) per week, the remaining 42 (43.8%) performed less than 10 vaccinations in a week; 16 HCPs worked in Belgian well-baby clinics.

3.2. HCPs practice

Of the 96 HCPs, 32 (33.3%) had previously received specific training on vaccine preparation and administration. The highest rates for specific training on vaccine preparation and administration were observed in nurses (8 nurses; 66.7%) and in HCPs who administered at least 10 vaccines per week (22 HCPs; 40.7%).

Almost all HCPs (95 HCPs, 99.0%) were typically involved in vaccine preparation and administration and 87 (90.6%) were typically involved in vaccine documentation. These results showed that, overall, HCPs were involved in the whole vaccination process. One nurse was not involved in vaccine administration and 9 GPs were not involved in documentation during the vaccination process.

Twelve HCPs (12.5%) had previously used a fully-liquid hexavalent vaccine.

HCPs had delivered paediatric vaccinations for a mean (SD) 17.2 years (12.3), delivering (preparation and/or administration) a mean (SD) of 16.1 vaccinations (15.7) per week. Among the delivered vaccinations, a mean (SD) of 15.3 vaccinations (15.9) were childhood vaccinations and among these, 8.8 (9.9) were hexavalent vaccinations (Table 2).

Table 1
Characteristics of the HCPs.

	Specialty			Number of vaccinations[a]		Total (*N* = 96)
	Nurses (*N* = 12)	Paediatricians (*N* = 50)	GPs (*N* = 34)	<10 (*N* = 42)	≥10 (*N* = 54)	
Age (years)						
Mean (SD)	43.4 (10.1)	50.0 (11.8)	36.9 (10.8)	40.0 (11.3)	48.1 (12.7)	44.5 (12.7)
Min; Max	28; 56	26; 73	27; 70	27; 70	26; 73	26; 73
Gender (%)						
Male	0.0	36.0	38.2	35.7	29.6	32.3
Female	100.0	64.0	61.8	64.3	70.4	67.7

[a] Average number of vaccinations performed by HCPs in a week.

3.3. Vaccine preparation time

The mean time (SD) needed to prepare the fully-liquid vaccine was 36.0 s (22.8) and the mean time (SD) needed to prepare the non-fully liquid vaccine was 70.5 s (33.2) (Fig. 2). The preparation-time difference between the two vaccines, i.e. the time saved with the fully-liquid vaccine, was 34.5 s [95% Confidence Interval (CI): 28.4; 40.6], $p < 0.001$. This difference was highest among GPs (46.3 s [95%CI: 30.9; 61.7]) and HCPs who performed less than 10 vaccinations per week (45.2 s [95%CI: 33.1; 57.3]). The time saving was statistically significant for the total HCP population, as well as for each subgroup studied (Table 3).

3.4. Immunisation errors

Overall, 57 immunisation errors were observed during the 192 vaccine preparations: 47 occurred with the non-fully liquid vaccine versus 10 with the fully-liquid vaccine (Table 4a–b). Mean difference in number of preparation mistakes was 0.39 (95%CI: 0.24; 0.53], $p < 0.001$).

With the non-fully liquid vaccine, mean (SD) number of immunisation errors tended to be higher in HCPs performing <10 than in HCPs performing ≥10 vaccinations per week with respectively 0.6 (0.7) vs. 0.4 (0.7) immunisation errors. Mean (SD) number of immunisation errors also tended to differ by HCP specialty: 0.3 (0.5) in nurses, 0.5 (0.6) in paediatricians and 0.6 (0.8) in GPs. With the fully-liquid vaccine, no difference was observed by number of vaccination performed per week; however, mean (SD) number of immunisation errors tended to be lower in paediatricians and GPs compared to nurses (respectively 0.1 (0.3) and 0.1 (0.2) vs. 0.3 (0.5)) (Table 4a).

The most frequently observed immunisation errors during preparation of the non-fully liquid vaccine were: lack of purge of syringe by the end of preparation (12 HCPs, 12.5%), syringe purged before using the second needle (11 HCPs; 11.5%), lack of replacement of the preparation needle by the administration needle at the end of vaccine preparation (8 HCPs, 8.3%) and the whole content of the Hib-PRP-T vial not aspired into the syringe (8 HCPs, 8.3%). In one case reconstitution of the content of the Hib-PRP-T vial was missed.

The most frequently observed error during preparation of the fully-liquid vaccine was: lack of purge of the syringe by the end of preparation (4 HCPs; 4.2%) (Table 4a–b).

Leakage of the non-fully liquid vaccine with skin contact but without any clinical consequence to the HCP was reported as an adverse event during the study.

3.5. HCPs satisfaction and preference

Sixty-nine HCPs (71.9%) were very or somewhat satisfied with ease of handlings of both vaccines; 64 HCPs (66.7%) and 65 HCPs (67.7%) were very or somewhat satisfied with speed of preparation of the fully-liquid vaccine and the non-fully liquid vaccine, respectively.

Among the 96 HCPs, preference for the vaccine form in childhood vaccination daily practice was assessed in 83 HCPs deemed to have sufficient experience in childhood vaccination (> 3 vaccinations a week). Almost all (97.6%) stated that they would prefer the use of a fully-liquid hexavalent vaccine in their daily practice.

4. Discussion

4.1. Vaccine preparation time

As expected, and consistently with previous results obtained in a clinical study conducted in HCPs working environment [2], preparation of the fully-liquid hexavalent vaccine took approximately 50% less time than required to prepare the non-fully liquid vaccine (36 s vs. 70.5 s). Time savings were more pronounced among less experienced HCPs (those performing less than 10 vaccinations

Table 2
Description of HCP experience in paediatric vaccination in total, by HCP specialty and by number of vaccination performed by HCPs in a week.

	Specialty			Number of vaccinations[a]		Total (*N* = 96)
	Nurses (*N* = 12)	Paediatricians (*N* = 50)	GPs (*N* = 34)	<10 (*N* = 42)	≥10 (*N* = 54)	
Numbers of years in practice in paediatric vaccinations						
Mean (SD)	17.3 (10.2)	21.9 (12.0)	10.1 (10.1)	12.9 (11.1)	20.4 (12.3)	17.2 (12.3)
Min; Max	3; 34	2; 46	2; 45	2; 45	2; 46	2; 46
Number of vaccinations (preparation and/or administration) personally managed a week						
Mean (SD)	15.3 (10.9)	21.3 (18.6)	8.7 (7.7)	5.2 (2.0)	24.5 (16.5)	16.1 (15.7)
Min; Max	4; 40	1; 75	2; 40	1; 9	10; 75	1; 75
Childhood vaccinations						
Mean (SD)	15.3 (10.9)	21.1 (18.5)	6.7 (7.3)	4.4 (2.4)	23.7 (16.7)	15.3 (15.9)
Min; Max	4; 40	1; 75	1; 37	1; 9	5; 75	1; 75
Hexavalent vaccinations						
Mean (SD)	8.6 (5.6)	12.3 (11.9)	3.6 (4.3)	2.6 (1.4)	13.5 (11.1)	8.8 (9.9)
Min; Max	3; 20	1; 55	1; 24	1; 5	2; 55	1; 55

[a] Average number of vaccinations performed by HCPs in a week.

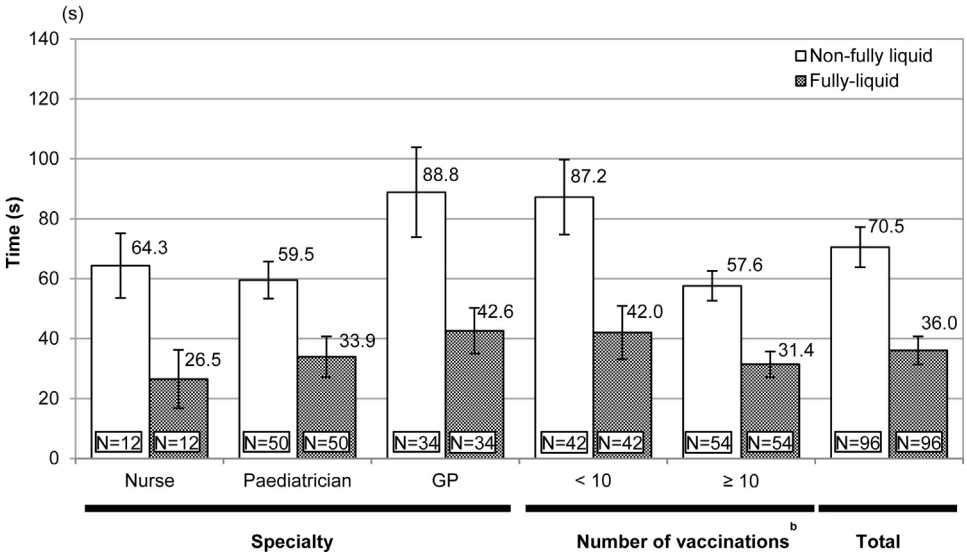

Fig. 2. Mean time necessary to prepare[a] the vaccine in total, by HCP specialty and by number of vaccinations performed in a week by HCPs. [a] Preparation time excluded time necessary to obtain vaccine from storage, administration of vaccine, disposal of vial, syringe, needle(s), and documentation of vaccine administration. [b] Average number of vaccinations performed by HCP in a week. Results are presented as mean ± 95% confidence intervals.

per week). Although time savings are expected to result in limited pragmatic differences at individual HCP practice level, when measured over large cohorts of vaccinees (e.g. at a country level) time savings can be significant.

4.2. Immunisation errors

Vaccination programmes seek high immunisation coverage across populations. The success of these programmes in protecting individuals and society depends on a number of factors, including the quality with which vaccines are administered [4]. According to the World Health Organization, adverse events following immunisation (AEFIs) due to programmatic errors in the storage, handling, or administration of vaccine are more common than AEFIs due to the properties of vaccines [11]. Preparation of the fully-liquid vaccine resulted in fewer immunisation errors as compared to the non-fully liquid vaccine since much more preparation steps are required with the latter. Although these results are not unexpected, and gathered in experimental circumstances, significant differences are likely to occur in real life conditions. Errors observed in this study during vaccine preparation could be divided in two main categories: errors that could result in health complications and errors reducing immunisation effectiveness. Safety problems with vaccines requiring reconstitution have been reported before [2]. During injecting drug preparation a variety of improper manipulations may compromise sterility, resulting in potential contamination of the end product [12]. A fully liquid vaccine needing less manipulations will reduce this risk. Bundy et al. proposed 'the 5 rights' of medicine administration (right patient, right medication, right dosage, right time, right route) to analyse reported vaccine errors [4,13,14]. Considering this, a fully liquid one dose vaccine will offer fewer opportunities for error by reducing the risk of wrong dosage as no contents have to be mixed or aspired out of vials and therefore can avoid incomplete aspiration or reconstitution failure. In this study 8 cases of incomplete aspiration of the Hib vial, 1 leakage and 1 reconstitution failure occurred, compromising as such a good immunisation. Comparison can be made with iv drug administration, where multiple step preparation, including reconstitution of a drug was identified as one of the contributing factors for errors [15]. In addition, the number of immunisation errors was higher in less experienced HCPs. While enhanced training is one of the potential strategies for reducing vaccination errors, the fact remains that depending of the setting not every HCP has the opportunity to improve his or her skills by practice: for instance, young HCPs with starting practices or settings where paediatric vaccination is less frequent. In these cases particularly, fully liquid one dose vaccines will optimise immunisation error reduction essential for patient safety and vaccine effectiveness.

4.3. HCPs satisfaction and preference

The satisfaction perceived by HCPs with regard to the ease-of-handling and the speed of preparation of both vaccines was similar. Often, someone's level of satisfaction is dependent on his

Table 3
Time savings with a fully-liquid vaccine compared to a non-fully liquid vaccine in total, by HCP specialty and by number of vaccination performed by HCPs in a week.

	Specialty			Number of vaccinations[a]		Total (*N* = 96)
	Nurses (*N* = 12)	Paediatricians (*N* = 50)	GPs (*N* = 34)	<10 (*N* = 42)	≥10 (*N* = 54)	
Time savings[b]						
Mean (SD)	37.8 (16.2)	25.6 (14.2)	46.3 (44.1)	45.2 (38.8)	26.2 (17.1)	34.5 (30.0)
[95% CI]	[27.6; 48.1]	[21.6; 29.7]	[30.9; 61.7]	[33.1; 57.3]	[21.5; 30.8]	[28.4; 40.6]
Min; Max	9; 63	−9; 66	−12; 195	−12; 195	−12; 105	−12; 195
Wilcoxon paired test						
p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

[a] Average number of vaccinations performed by HCPs in a week.
[b] Mean time needed to prepare non-fully liquid vaccine minus mean time needed to prepare fully liquid vaccine.

Table 4
(a) Immunisation errors occurred during non-fully liquid and fully liquid vaccine preparation. (b) Immunisation errors during non-fully liquid and fully liquid vaccine preparation: detailed information.

Immunisation errors (a)

	Non-fully liquid		Fully liquid	
Number of immunisation errors per HCP	Mean (SD)	Min; Max	Mean (SD)	Min; Max
Total (*N* = 96)	0.5 (0.7)	0; 3	0.1 (0.3)	0; 1
Specialty				
Nurse (*N* = 12)	0.3 (0.5)	0; 1	0.3 (0.5)	0; 1
Paediatrician (*N* = 50)	0.5 (0.6)	0; 2	0.1 (0.3)	0; 1
GP (*N* = 34)	0.6 (0.8)	0; 3	0.1 (0.2)	0; 1
Number of vaccines administered[a]				
<10 (*N* = 47)	0.6 (0.7)	0; 2	0.1 (0.4)	0; 1
≥10 (*N* = 54)	0.4 (0.7)	0; 3	0.1 (0.3)	0; 1

Type of immunisation errors (*N* = 96)	*n* (%)	*n* (%)
No purge by the end of preparation	12 (12.5)	4 (4.2)
Purge performed before using the second needle	11 (11.5)	2 (2.1)
Non-fully liquid vaccine prepared using only one needle	8 (8.3)	–
Whole content of the vial not aspired into the syringe	8 (8.3)	–
Other	8 (8.3)	4 (4.2)
Total number of immunisation errors (*n*)	47	10

Immunisation errors (b)

	Non-fully liquid (*N* = 96)	Fully liquid (*N* = 96)	Total (*N* = 192)
Immunisation errors as defined in the protocol	n (%)	n (%)	n (%)
HCP fingers touched the vial rubber cap after removal of the protective plastic cap	2 (2.1%)	0 (0.0%)	2 (1.0%)
HCP fingers touched the top of the syringe after removal of the protective cap	0 (0.0%)	0 (0.0%)	0 (0.0%)
HCP fingers touched sterile part of the needle used for reconstitution or injection	1 (1.0%)	1 (1.0%)	2 (1.0%)
Liquid leakage during preparation	1 (1.0%)	0 (0.0%)	1 (0.5%)
Haemophilus influenza type B (Hib) reconstitution missed	1 (1.0%)	0 (0.0%)	1 (0.5%)
Syringe has not been purged by the end of the preparation process	12 (12.5%)	4 (4.2%)	16 (8.3%)
Needle stick during vaccine preparation	0 (0.0%)	0 (0.0%)	0 (0.0%)
Prepared using one needle only	8 (8.3%)	0 (0.0%)	8 (4.2%)
HCP did not aspire the whole content of Hib vial in the syringe	8 (8.3%)	0 (0.0%)	8 (4.2%)
Other observed immunisation errors	n (%)	n (%)	n (%)
Changed the needle before drawing up the liquid- 2 needles were used but the same needle was used for reconstitution and injection	1 (1.0%)	0 (0.0%)	1 (0.5%)
HCP recapped the syringe with a rubber that touched the tray–Purged 2 times but not at the end- Needle changed 3 times	0 (0.0%)	1 (1.0%)	1 (0.5%)
Purge performed before using the second needle	11 (11.5%)	2 (2.1%)	13 (6.8%)
Purge performed before assembling needle and syringe	0 (0.0%)	2 (2.1%)	2 (1.0%)
Syringe was put down on the tray–risk of contamination at the tip	1 (1.0%)	0 (0.0%)	1 (0.5%)
The needle twisted when it was inserted in the vial stopper	1 (1.0%)	0 (0.0%)	1 (0.5%)

"*N*" is the number of vaccine preparations performed for each form of the vaccine. "*n*" is the number of immunisation errors observed. "–" Type of mishandling that cannot occur during fully liquid vaccine preparation.

[a] Average number of vaccines administered by HCPs in a week.

expectations. The two vaccines have different characteristics and it is reasonable to consider that HCPs had different expectations for each vaccine, especially for a vaccine that is new on the market. However, almost all HCPs would prefer using the hexavalent vaccine in their childhood vaccination daily practice as fully-liquid vaccine in prefilled syringe. Even though preference is subjective, the involvement of participating HCPs in the whole vaccination process lends credibility to the preference they expressed.

4.4. Limitations of the study and external validity of the findings

Although this study was conducted in only one European country, it can be assumed that childhood vaccine preparation practices are similar from one country to another. Therefore, time savings with the fully-liquid vaccine highlighted in this study can be generalised to other countries (i.e. a 50% reduction in comparison to the non-fully liquid vaccine). There are, however, possible differences in local practices, cultural preferences for specific pharmaceutical forms and also specific organisation of vaccine delivery in other countries, which may impact the generalisation of preference of HCPs for the fully-liquid vaccine.

5. Conclusions

Fully-liquid hexavalent vaccine reduced significantly the preparation time as compared to non-fully liquid hexavalent vaccine that needs more steps for reconstitution of the vaccine. This can have significant impact when considering large number of vaccination processes. Lastly, reducing steps in the vaccine preparation workflow decreases the opportunities for immunisation errors and thus might impact safety.

Conflict of interest statement

Ilse De Coster and Pierre Van Damme act as investigators for vaccine trials conducted on behalf of the University of Antwerp, for which the University obtains research grants from vaccine manufacturers; speakers fees for presentations on vaccines are paid directly to an educational fund held by the University of Antwerp. Ilse De Coster and Pierre Van Damme did not receive personal remuneration for this work. Céline Faure and Xavier Fournie are full-time employees of Mapi, which was contracted by SPMSD to conduct the study. Eddy Ziani, Laurence Nicolas and Benoit Soubeyrand are full-time employees of SPMSD.

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